revised claims. All the claims in the Response after Final from the immediate parent are in this application.

In any of the predecessor applications, no restriction requirements were made, and the subject matter encompassed both the (TGF-β2) and the β3 (TGF-β3) products. It is emphasized that the process for making each, whether (TGF-β2) or β3 (TGF-β3), is the same. The starting materials only differ. The Examiner can readily search both inventions. It is also pointed out that a voluminous search and the prior art references from both parent applications and any corresponding foreign applications have been cited in the instant application.

The Applicants contend the subject matter of the individual Groups is interrelated and shares common subject matter. The division of the subject matter is believed to place an unreasonable burden on Applicants. A single unified search of the subject matter of all the Claims has been already performed satisfactorily centered about the subject matter of the Groups I and II claims. It is believed that such a search would be of a suitable scope, and may be performed without being unduly burdensome on the part of the Office. Accordingly, reconsideration of the Restriction Requirement entered is solicited, and a single-coextensive search of the subject matter of the claims requested. An action upon the merits of all of the outstanding Claims is anticipated in the next communication to Applicants.

The Examiner would also appear to have to search both groups II and I as defined within the restriction requirement to examine the application.

To further the prosecution of this application, Applicant's attorney provides the following discussion of the closest prior art and issues as most recently submitted in the immediate parent application.

REMARKS

The Claims in the case are Claims 19-25. These claims concisely claim Applicant's invention for which patent protection is sought, and to avoid any obviousness and novelty issues

Section 112 issue

The predecessor claims corresponding to Claims 21 and 22 had been rejected in USSN 09/316,724 under 35 USC § 112, second paragraph. The Examiner had then suggested

amendments to the claim language as a way to avoid the rejection. This language is present in Claims 21 and 22. These claims are urged as patentable without any issues under Section 112.

No other rejections under Section 112 were against the claims in the parent application USSN 09/316,724.

SECTION 102 and SECTION 103 rejection

This invention is the present application relates to a method of folding TGF-β's (whether (TGF-β2) or β3 (TGF-β3), using a water miscible solvent, such as DMSO, $DMSO_2$, DMF etc. without the presence of the mild detergent such as CHAPS or CHAPSO, and further in the absence of a chaotropic agent and in the presence of a reduced glutathione.

The Examiner had rejected Claims in the parent application USSN 09/316,724 under 35 USC § 102 (e), as anticipated by Builder, US 5 407 810. The Examiner had also rejected Claims as being unpatentable over Builder, US 5 407 810, 35 USC § 103 (a).

The Builder patent, US 5 407 810 has its main emphasis on a multi-phase extraction procedure. It also covers a folding process in which a solubilized protein, such as TGF-beta, is treated with a folding buffer that comprises a polar aprotic buffer, including DMSO or DMF. In addition, however, the Builder folding buffer comprises a number of additional essential components, including about 0.1 to 9M of a chaotropic agent and about 0.01 to 17 microM of a copper or manganese salt.

Applicant's invention does not use either of these two latter components in the folding buffer, at least for TGF-beta 3. There is acetic acid in the TGF-beta solution which is then mixed with the folding buffer. However, the acetic acid solution which is used by Applicant, (see Example 3-5 of the application) does not amount to presence of a chaotropic agent in the buffer. It provides acidic conditions for solubilization. Solution fractions containing the solubilized acidified monomeric TGF-ß are then directly subjected to in vitro folding, but the folding solution does not contain a chaotropic agent.

Applicant also does not add Cu or Mn salt, which have as their general purpose, the facilitation of the generation of disulfides, e.g., cystines from the reduced cysteine sulfhydryl groups. Instead, Applicant employs a 5 mM reduced glutathione. Because of its chemical nature (free sulfhydryl group), this agent facilitates disulfide formation by a different chemical mechanism,

catalysis of sulfhydryl/disulfide interchange, quite unobvious from the method used in Builder.

The conditions described are present in the Claims 19-25 pending in the instant application, which, it is urged, are patentable over the art.

OBVIOUSNESS-TYPE DOUBLE PATENTING rejection

The Claims in the parent application were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending application USSN 09/123 233, which is issued as US Patent 6 057 430. Applicant filed a terminal disclaimer of any portion of the term of a patent from the instant application over the term of the US Patent 6 057 430, and a copy of those papers, which were separately filed on January 17, 2001, were in the record of the parent application. Therefore this issue against the claims is no longer relevant.

Conclusion

In view of the foregoing, Applicant submits the Application is now in condition for allowance and respectfully requests early notice to that effect.

Should the Examiner feel that telephonic communication with Applicants' representative would further the prosecution of the instant application, he is invited to telephone the undersigned.

No fees are believed due with this amendment; if however, any fees are due, please charge such fees to Deposit Account No. 19-0134 in the name of Novartis Corporation.

Respectfully submitted,

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